

### Remarks

Claims 39-43 were pending in this application and stood rejected on various grounds. Claim 44 was canceled previously. Applicants hereby cancel claims 39-43 without prejudice or disclaimer and add new claims 45 to 49. Claim 45 recites a method for diagnosing lung or colon cancer, support for which can be found in previous claim 39 and in the specification, at least in Example 92. Although the Examiner has withdrawn prior rejections to previous claims under 35 USC § 112, second paragraph, all claims remained rejected under 35 USC § 101/112 for alleged lack of utility/ for alleged lack of enablement and written description, and under 35 USC § 102(b) and 103.

Applicants address these rejections as applied to the new claims, and respectfully traverse the rejections.

### Priority

As will be apparent from the discussions below and from the Declaration by Dr. Avi Ashkenazi filed under 37 C.F.R. § 1.132, Applicants submit that the results of the gene amplification assay provide specific and substantial asserted utility for the antibodies claimed in the present application. In addition, Applicants submit that both the International application PCT/US99/30095 filed December 16, 1999, published as WO 00/37640 (support is present at least at pages 133-137, pages 154-155 and pages 116-121 of the WO 00/37640 publication) and US provisional application 60/113296, filed December 22, 1998 support the claims pending in this application. For the Examiner's convenience, along with the present response, Applicants provide a copy of the US provisional application 60/113296 filed December 22, 1998, where support is, for example, at page 23, last paragraph or Table 2.

Thus, all claims are entitled to the priority of December 22, 1998 of provisional application Serial No. 60/113,296 filed on 22 December 1998.

### Claim Rejections – 35 USC § 101/112

Claims 39-43 were rejected under 35 USC § 101, first paragraph, for alleged lack of

utility/enablement. These rejections are addressed as applied to new claims 45 to 49.

The Examiner asserts that "the increased copy number of DNA does not provide a readily apparent use for the polypeptide, because there is no information regarding the level of expression, an activity, or a role in cancer for the polypeptide or the claimed antibody which binds to said polypeptide." Citing Pennica *et al.*, the Examiner adds that "it does not necessarily follow that a increase in gene copy number results in increased gene expression and increased protein expression, such that the antibodies would be useful diagnostically or as target for cancer drug development." From this, the Examiner concludes that the PRO343 polypeptide and antibodies binding to such polypeptide lack specific or substantial utility. For the same reasons, the Examiner also concludes that one of skill in the art would not know how to use the claimed antibodies.

Applicants respectfully disagree.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.

Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

*A prima facie case of lack of utility has not been established*

The Examiner bases the conclusion of lack of utility on a quote from Pennica *et al.*, submitted as Exhibit D of the Goddard Declaration filed with applicants' response to the prior Office Action. According to the quoted statement, WISP-1 gene amplification in human colon tumors correlated with over-expression; WISP-3 RNA was over-expressed in the absence of gene amplification; and WISP-2 DNA was amplified in colon tumors, while its mRNA was reduced in the majority of tumors. From this, the Examiner correctly concludes that increased copy number does not necessarily result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack of correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

*Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence*

Even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility. Enclosed is a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr Ashkenazi explains, even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-

expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Accordingly, the PRO343 polypeptide and antibodies binding to it have a substantial specific utility, and the present rejection should be withdrawn.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejections to claims 45-49.

Claim Rejections - 35 USC § 102

Claims 39-40, 42-43 were rejected under 102 (b) as allegedly being anticipated by Amrad Operations Pty. Ltd. (WO98/36054; pub 20 August 1998). Again, the rejections are addressed as applied to new claims 45 to 49.

Claim 45 recites a method for detecting lung or colon cancer. Since the Amrad reference does not teach that the PRO343 polypeptide is a marker of lung or colon cancer, it does not anticipate the current claims.

Thus, Applicants respectfully request withdrawal of this rejection.

Claim Rejections - 35 USC § 103

Claims 39 and 41 were rejected under 103 (a) as allegedly being unpatentable over Amrad Operation Pty. Ltd. (WO98/36054; pub 20 August 1998) in view of Carter (U.S.P. N. 5,821,337). Again, the rejections are addressed as applied to new claims 45 to 49.

As evidenced above, since the primary reference by Amrad Operation Pty. Ltd. does not anticipate current claims, the rejection under 103(a) falls. In addition, Carter does not teach that the PRO343 polypeptide is a marker of lung or colon cancer.


Accordingly, Applicants submit that currently pending claims 45 to 49 are not obvious over WO98/36054 in view of Carter (U.S.P. N. 5,821,337) and request withdrawal of this rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C49). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 22, 2003

  
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9/22/03 9:04 AM (39780.1618)